

REMARKS

Claims 1-43 and 49-50 stand cancelled. Claims 43-46 and 51 have been amended. No new matter has been added by virtue of these amendments; support therefor being found throughout the specification and in the original claims of the application.

Rejection under 35 USC §112, second paragraph

Claim 46 stands rejected under 35 USC §112, second paragraph, for its recitation of "each of R¹ and R² represents a C₁₋₆ alkyl; R¹ and R² are the same as each other" (and a similar recitation for R⁷ and R⁸).

Applicant has amended claim 46 to clarify these aspects of the invention. For instance, the claim now recites that "each of R¹ and R² independently represent a C₁₋₆ alkyl. The latter phrase "R¹ and R² are the same as each other" has been stricken. Similar amendments were made relative to the recitation for R⁷ and R⁸.

Applicant respectfully submits that the within amendments obviate the rejection under 35 USC §112, second paragraph. Withdrawal of the rejection is therefore requested.

Rejection under 35 USC §112, first paragraph

Claims 43-48, 51 and 52 stand rejected under USC 35 §112, on the grounds of enablement (for prevention) and scope of enablement (for both compounds and diseases).

With respect to the first grounds for rejection, objection is made to the recitation of the term "prevention". Applicant has amended claims 43-45

without prejudice or disclaimer to remove that term. As amended, the claim recites now "A method for the acute or prophylactic treatment...". Claims 46-48, 51 and 52 depend from the presently amended claims. Thus, it is respectfully submitted that the amendment to claims 43-45 obviates the rejection of those claims as well. The amendment is amply supported in the specification, for example at page 20, line 17 to page 21, line 2, where it is stated that:

Compounds of the present invention are PDE inhibitors and thus possess valuable pharmacological properties, such as bronchodilator activity as demonstrated by the inhibition of field-stimulated contraction of guinea-pig isolated trachea, and anti-inflammatory activity as illustrated in studies on human mononuclear cells stimulated by PHA (phytohaemagglutinin). In vitro and in vivo data indicate the compounds have a long duration of action, as demonstrated by their persistent protective effects against histamine induced bronchospasm in the guinea-pig when inhaled directly into the lungs as a dry powder. The invention therefore also relates to acute, chronic or prophylactic treatment of patients suffering from respiratory disorders including, in particular, asthma, allergic asthma, hay fever, allergic rhinitis, bronchitis, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), and cystic fibrosis. They may also be used topically in skin disorders such as atopic dermatitis and psoriasis, or in ocular inflammation or any other disease including cerebral ischaemia or auto-immune diseases in which increasing intracellular concentrations of cAMP is considered beneficial.

Thus, it is respectfully submitted that the first grounds of the enablement rejection be withdrawn.

Claims 43-48 and 51 also stand rejected under 35 USC 112, first paragraph, on the grounds of scope of enablement. In one aspect of this rejection, the Office Action expressly acknowledges that the specification is enabling for a method of treating asthma or COPD using compounds of formula I wherein X is CR^3R^4 . However the position is taken that enablement is lacking for those embodiments wherein X is OCH_2 .

In order to expedite allowance of the present application, claims 43-45 have been amended to limit X to CR³R⁴. Such amendment is submitted without prejudice or disclaimer and the right to pursue further prosecution of the cancelled subject-matter is reserved. Claims 46-48 and 51 depend from the presently amended claims. Thus, it is respectfully submitted that the amendment to claims 43-45 obviates this aspect of the rejection with respect to claims 46-48 and 51 as well. It is respectfully submitted, therefore, that the rejection be withdrawn.

In another aspect of the enablement rejection, claim 43 stands further rejected and it is alleged that the scope of that claim is overly broad in terms of diseases.

Applicant respectfully requests clarification regarding the subject-matter that the Examiner is rejecting in this rejection. In any event, the rejection is traversed. Applicant submits that the diseases encompassed in the claim are all diseases in which increasing intracellular concentrations of cAMP is considered beneficial. Again, attention is directed to page 20, line 17 to page 21, line 2 (reproduced above). As explained in that passage, the invention is useful for any number of diseases in which increasing intracellular concentrations of cAMP is considered beneficial.

While the list of diseases is somewhat extensive, one skilled in the art would readily understand that the instant invention, because of its mode of action, would be effective in treating or inhibiting each of the listed diseases. Accordingly, Applicant respectfully submits that the breadth of the claims is proper in that the specification - and level of skill in the art - provides sufficient enablement for the skilled artisan to practice the full scope of the invention.

Claims 43-48 and 51 stand further rejected under 35 USC §112, first paragraph. It is alleged that the specification fails to provide sufficient enablement for diseases such as atopic dermatitis, psoriasis, ocular inflammation, cerebral ischaemia and cystic fibrosis etc. As this aspect of the rejection is understood, the reason is that the application provides no *in vivo* tests on the skin, eyes, brain, and the like.

Again, the rejection is traversed. Applicant respectfully submits that there is ample support and enablement for the treatment or inhibition of cystic fibrosis, as this disease comprises a respiratory component.

For instance, attention is directed to *Example B* at page 56, line 4 to page 57, line 8 and Figure 8. This example shows that the present invention reduces the level of mononuclear cells in human subjects. In particular, the efficacy of a compound of the invention is investigated against proliferation of human mononuclear cells stimulated by PHA.

As shown in this example and the noted Figure, proliferation was significantly inhibited by the compound, indicating that it possesses anti-inflammatory activity. The result serves to illustrate the generic application of the novel compounds of the present invention.

Additionally, as would be known to one skilled in the art, there is a well documented and readily understood relationship between atopic dermatitis and elevated mononuclear cells. Treatments that reduce the levels of mononuclear cells are effective in treating and inhibiting atopic dermatitis.

Further, the relationship between psoriasis and elevated levels of mononuclear cells is also well known and documented. Treatments that

reduce the levels of mononuclear cells are effective in treating and inhibiting psoriasis.

Similarly, the relationship between ocular inflammation and mononuclear cells is well known and documented. Treatments that reduce the levels of mononuclear cells are effective in treating and inhibiting ocular inflammation.

Still further, the relationship between cerebral ischemia and mononuclear cells is well known and documented. Treatments that reduce the levels of mononuclear cells are effective in treating and inhibiting cerebral ischemia.

Accordingly, given the enabling specification, the claimed compounds and the substance of Example B, one skilled in the art would have sufficient direction and guidance to practice the full scope of the present invention without undue experimentation.

In rejecting claims 43-48 and 51, it is also alleged that the state of the prior art does not overcome the deficiency in the enablement provided by the present application. In a further effort to advance the application, Applicants have amended the claims, as described above, to delete the tricyclic system in which X is OCH₂.

It is believed that no further amendments to the claims are needed to overcome the various aspects of the enablement rejection. However, in the event that the within arguments are insufficient to persuade the Examiner as to the enablement issues, Applicants kindly request further clarification as to the subject-matter that is rejected per these grounds so that Applicants can address same with even more particularity.

Applicant respectfully submits that the within amendments obviate each of the rejections under 35 USC §112, first paragraph. Withdrawal of the rejections is therefore requested.

In view of the above arguments and the within amendments, Applicant believes the pending application is in condition for immediate allowance, which action is earnestly solicited.

Dated: August 12, 2005

Respectfully submitted,

By



Christine C. O'Day

Registration No.: 38,256

EDWARDS & ANGELL, LLP

P.O. Box 55874

Boston, Massachusetts 02205

(617) 439-4444

Attorneys/Agents For Applicant